

WHAT IS CLAIMED IS:

1 1. A method of treating a neoplasia in a mammal, said method
2 comprising administering to said mammal a serum-stable nucleic acid-lipid particle
3 comprising a nucleic acid portion that is fully encapsulated within the lipid portion,
4 wherein said administration is by injection at an injection site that is distal to said
5 neoplasia in said mammal.

1 2. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid comprises an expressible gene.

1 3. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said expressible gene encodes a member selected from the group
3 consisting of therapeutic polypeptides and therapeutic polynucleotides.

1 4. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said gene is exogenous.

1 5. A method of treating a neoplasia in a mammal in accordance with
2 claim 3, wherein said gene is a member selected from the group consisting of genes
3 encoding suicide enzymes, toxins and ribozymes.

1 6. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said gene encodes a member selected from the group consisting of
3 herpes simplex virus thymidine kinase (HSV-TK), cytosine deaminase, xanthine-
4 guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450
5 2B1 and analogs thereof.

1 7. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said gene is homologous.

1 8. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said gene encodes a member selected from the group consisting of
3 proto-oncogenes, cytokines, immune stimulatory proteins and anti-angiogenic proteins.

1 9. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein said gene is a member selected from the group consisting of IL-2, IL-12,
3 IL-15 and GM-CSF.

1 10. A method of treating a neoplasia in a mammal in accordance with
2 claim 2, wherein a therapeutically effective amount of said gene is generated at said
3 neoplasia.

1 11. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid-lipid particle comprises a protonatable lipid having a
3 pKa in the range of about 4 to about 11.

1 12. A method of treating a neoplasia in a mammal in accordance with
2 claim 11, wherein said protonatable lipid is a member selected from the group consisting
3 of DODAC, DODAP, DODMA, DOTAP, DOTMA, DC-Chol, DMRIE, DSDAC and
4 mixtures thereof.

1 13. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid-lipid particle comprises a lipid conjugate that prevents
3 aggregation during formulation.

1 14. A method of treating a neoplasia in a mammal in accordance with
2 claim 13, wherein said lipid conjugate is a member selected from the group consisting of
3 PEG-lipids and PAO-lipids.

1 15. A method of treating a neoplasia in a mammal in accordance with
2 claim 13, wherein said lipid conjugate is reversibly associated with an outer lipid
3 monolayer, and wherein said lipid conjugate exchanges out of said outer lipid monolayer
4 at a rate faster than PEG-CerC20.

1 16. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid-lipid particle is substantially devoid of detergents and
3 organic solvents.

1 17. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein a therapeutically effective amount of said nucleic acid-lipid particle
3 accumulates at said neoplasia.

1 18. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein a therapeutic effect is detected at the site of said neoplasia.

1 19. A method of treating a neoplasia in a mammal in accordance with
2 claim 17, wherein said therapeutically effective amount comprises greater than about
3 0.5% of an administered dose.

1 20. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid-lipid particle has a diameter of about 50 nm to about
3 200 nm.

1 21. A method of treating a neoplasia in a mammal in accordance with
2 claim 20, wherein said nucleic acid-lipid particle has a diameter of about 60 nm to about
3 130 nm.

1 22. A method of treating a neoplasia in a mammal in accordance with
2 claim 20, wherein said nucleic acid-lipid particles are of a uniform size.

1 23. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid-lipid particle has a nucleic acid to lipid ratio of greater
3 than about 3 mg nucleic acid to mmole of lipid.

Sub E 1
2 24. A method of treating a neoplasia in a mammal in accordance with
3 claim 23, wherein said particle has a nucleic acid to lipid ratio of greater than about 14
mg nucleic acid to mmole of lipid.

1 25. A method of treating a neoplasia in a mammal in accordance with
2 claim 23, wherein said particle has a nucleic acid to lipid ratio of greater than about
3 25 mg nucleic acid to mmole of lipid.

1 26. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said nucleic acid remains at least 90% intact when said particle

Sub E1
3 containing about 1 µg DNA is treated with about 100 U DNase 1 in digestion buffer at
4 37°C for 30 min.

1 27. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, further comprising administering a chemotherapeutic agent.

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1 28. A method of treating a neoplasia in a mammal in accordance with
2 claim 1, wherein said administering is performed at least once per eight weeks.

1 29. A method of sensitizing a neoplastic cell to a compound, said
2 method comprising:

3 a) transfecting said neoplastic cell with a serum-stable nucleic
4 acid-lipid particle encoding a gene-product comprising a nucleic acid that is fully
5 encapsulated within a lipid, wherein administration of said nucleic acid-lipid particle is by
6 injection at an injection site that is distal to said neoplastic cell; and

7 b) delivering to said cell a first compound which is processed
8 by said gene-product into a second compound, wherein said cell is more sensitive to said
9 second compound than said first compound.

1 30. A method of sensitizing a neoplastic cell in accordance with
2 claim 29 wherein said first compound is formulated in a lipid.

1 31. A method of sensitizing a neoplastic cell in accordance with
2 claim 29 wherein said gene product is a member selected from the group consisting of
3 therapeutic polypeptides and therapeutic polynucleotides.

1 32. A method of sensitizing a neoplastic cell in accordance with
2 claim 29 wherein said gene product is a member selected from the group consisting of
3 suicide enzymes, toxins and ribozymes.

1 33. A method of sensitizing a neoplastic cell in accordance with claim
2 29 wherein said gene product is a member selected from the group consisting of herpes
3 simplex virus thymidine kinase (HSV-TK), cytosine deaminase, xanthine-
4 guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450
5 2B1 and analogs thereof.

- 1 34. A method of sensitizing a neoplastic cell in accordance with
2 claim 29 wherein a therapeutic effect is detected at the site of said neoplasia cell.

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